Amendments to the Specification

Please replace the paragraph bridging lines 7-12 on page 1 with the following new paragraph:

This patent is a divisional of U.S. Application Serial No. 09/570,731 (filed on May 12, 2000), which, in turn, is a continuation-in-part of U.S. Application Serial Nos. 09/311,837 (filed on May 14, 1999) and 09/256,948 (filed on February 24, 1999). U.S. Application Serial No. 09/311,837 claims priority as a continuation-in-part of U.S. Application Serial Nos. 09/256,948, 09/191,129 (filed on November 13, 1998), and 09/186,410 (filed on November 5, 1998); and also claims priority to U.S. Provisional Application Serial Nos. 60/066,007 (filed on November 14, 1997), 60/095,347 (filed on August 4, 1998), 60/095,501 (filed on August 6, 1998), and 60/101,080 (filed on September 18, 1998). U.S. Application Serial No. 09/256,948 claims priority as a continuation-in-part of U.S. Application Serial Nos. 09/191,129 and 09/186,410; and also claims priority to U.S. Provisional Application Serial Nos. 60/066,007, 60/095,347, 60/095,501, and 60/101,080. U.S. Application Serial No. 09/191,129 claims priority as a continuation-in-part of U.S. Application Serial No. 09/186,410; and also claims priority to U.S. Provisional Application Serial Nos. 60/066,007, 60/095,347, 60/095,501, and 60/101,080. And U.S. Application Serial No. 09/186,410 claims priority to U.S. Provisional Application Serial Nos. 60/066,007, 60/095,347, 60/095,501, and 60/101,080. The entire text of each of the above-referenced patent applications are incorporated by referenced into this patent.

Please replace the paragraph bridging lines 15-25 on page 1 with the following new paragraph:

This invention is directed to proteinase (protease) inhibitors, and more particularly to the use of aromatic sulfone hydroxamic acid compounds (including hydroxamates) that, *inter alia*, are selective inhibitors of matrix metalloproteinases in a process for treating conditions associated with pathological matrix metalloproteinase activity, the selective inhibitors themselves, compositions of proteinase inhibitors, intermediates for the syntheses of proteinase inhibitors, and processes for the preparation of proteinase inhibitors.

Please replace the paragraph bridging lines 1-14 on page 4 with the following new paragraph:

TNF-α convertase is a metalloprotease involved in the formation of soluble TNF-α. Inhibition of TNF-α convertase (TACE) inhibits production of active TNF-α. Compounds that inhibit both MMPs activity and TNF-α production have been disclosed in WIPO International Publication Nos. WO 94/24140, WO 94/02466 and WO 97/20824. Compounds that inhibit MMPs such as collagenase, stromelysin and gelatinase have been shown to inhibit the release of TNF (Gearing et al. *Nature*, 370, 555-557 (1994), McGeehan et al., *Nature*, 370, 558-561 (1994)). There remains a need for effective MMP inhibitors. There also remains a need for effective TNF-α convertase inhibiting agents.

Please replace the paragraph bridging line 30 on page 4 to line 13 on page 5 with the following new paragraph:

Inhibition of selected MMPs can also be desirable in other instances. Treatment of cancer and/or inhibition of metastasis and/or inhibition of angiogenesis are examples of approaches to the treatment of diseases wherein the selective inhibition of stromelysin, gelatinase A or B, or collagenase III appear to be the relatively most important enzyme or enzymes to inhibit especially when compared with collagenase I (MMP-1). A drug that does not inhibit collagenase I can have a superior therapeutic profile. Osteoarthritis, another prevalent disease wherein it is believed that cartilage degradation of inflamed joints is at least partially caused by MMP-13 released from cells such as stimulated chrondrocytes, may be best treated by administration of drugs one of whose modes of action is inhibition of MMP-13. See, for example, Mitchell et al., *J. Clin. Invest.*, 97(3):761-768 (1996) and Reboul et al., *J. Clin. Invest.*, 97(9):2011-2019 (1996).

Please replace the paragraph bridging line 28 on page 5 to line 5 on page 6 with the following new paragraph:

Thiol group-containing amide or peptidyl amide-based metalloprotease (MMP) inhibitors are known as is shown in, for example, WO 95/13289, WO 96/11209 and U.S. 4,595,700. Hydroxamic acid group-containing MMP inhibitors are disclosed in a number of published

patent applications such as WO 95/29892, WO 97/24117, WO 97/49679 and EP 0 780 386 that disclose carbon back-boned compounds, and WO 90/05719, WO 93/20047, WO 95/09841 and WO 96/06074 that disclose hydroxamic acids that have a peptidyl back-bones or peptidomimetic back-bones, as does the article by Schwartz et al., *Progr. Med. Chem., 29:*271-334(1992) and those of Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997) and Denis et al., *Invest. New Drugs, 15*: 175-185 (1997).

Please replace the paragraph bridging lines 6-19 on page 6 with the following new paragraph:

One possible problem associated with known MMP inhibitors is that such compounds often exhibit the same or similar inhibitory effects against each of the MMP enzymes. For example, the peptidomimetic hydroxamic acid nown as batimastat is reported to exhibit IC_{50} values of about 1 to about 20 nanomolar (nM) against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat, another peptidomimetic hydroxamic acid was reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum very similar to batimastat, except that marimastat exhibited an IC_{50} value against MMP-3 of 230 nM. Rasmussen et al., *Pharmacol. Ther., 75(1)*: 69-75 (1997).

Please replace the paragraph bridging lines 5-12 on page 7 with the following new paragraph:

International application WO 98/38163, published on September 3, 1998 disclose a large group of hydroxamic acid inhibitors of MMPs and TACE. The compounds of WO 98/38163 contain one or two substituents adjacent to the hydroxamic acid functionality and a substituent that can be an aromatic sulfonyl group adjacent to those one or two substituents.

Please replace the paragraph bridging lines 13-18 on page 7 with the following new paragraph:

International application WO 98/37877, published on September 3, 1998 discloses compounds that contain a 5- to 7-membered heterocyclic ring adjacent to the hydroxamic acid functionality and can contain an aromatic sulfonyl group adjacent to the heterocyclic ring.

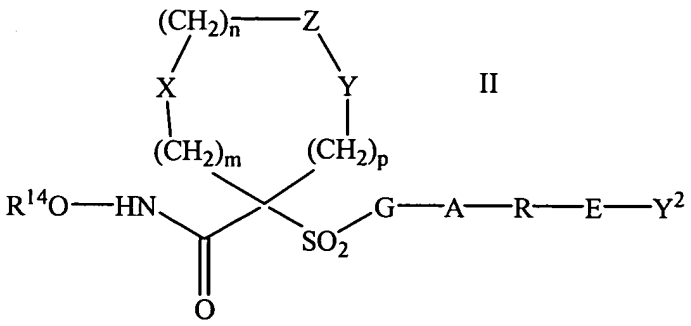
Please replace the paragraph bridging line 19 on page 7 to line 4 on page 8 with the following new paragraph:

Although many of the known MMP inhibitors such as batimastat, marimastat and the hydroxamic acids of WO 98/37877 and WO 98/38163 exhibit a broad spectrum of activity against MMPs, those compounds are not particularly selective in their inhibitory activity. This lack of selectivity may be the cause of the musculoskeletal pain and stiffness observed with their use. In addition, it can be therapeutically advantageous to utilize a medicament that is selective in its activity as compared to a generally active material so that treatment can be more closely tailored to the pathological condition presented by the host mammal. The disclosure that follows describes a process for treating a host mammal having a condition associated with pathological matrix metalloprotease activity that utilizes a compound that selectively inhibits one or more MMPs, while exhibiting less activity against at least MMP-1.

Please replace the paragraph bridging line 30 on page 12 to line 2 on page 13 with the following new paragraph:

Preferably, the R^3 substituent is Ph-Q-A-R-E-Y^2 wherein Ph is phenyl substituted at the 4-position relative to the depicted SO_2 group, and -Q-A-R-E-Y^2 is a substituent in which Q is a 5- to 7-membered heterocyclic ring containing one or two nitrogen atoms, one of which is bonded the depicted phenyl group, and whose remaining members are defined hereinafter for the substituent G-A-R-E-Y^2.

Please replace Formula II at line 1 on page 16 with the following new Formula II:



Please replace the paragraph bridging line 27 on page 21 to line 4 on page 22 with the following new paragraph:

G-A-R-E-Y^2 is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-Y^2 preferably has a length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

Please replace the paragraph bridging lines 24-25 on page 23 with the following new paragraph:

(9) E is absent and R is bonded directly to Y^2; and

Please replace the paragraph bridging line 26 on page 23 to line 10 on page 24 with the following new paragraph:

the moiety Y^2 is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl, aralkyl, or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, trifluoroalkyl, trifluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

Please replace the paragraph bridging lines 20-23 on page 24 with the following new paragraph:

m, n, p, X, Z, Y and R^{14} are as defined above for formula II, and the R^3 radical that is defined below is a sub-set of the previously discussed G-A-R-E-Y^2 substituents.

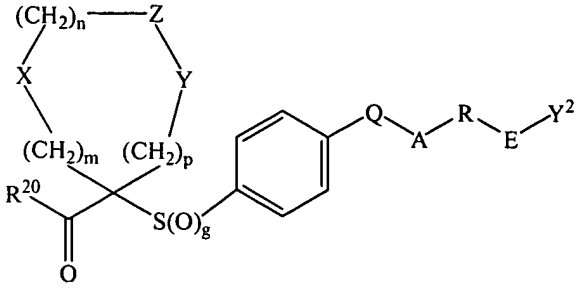
Please replace the paragraph bridging lines 3-6 on page 26 with the following new paragraph:

wherein R^3 is as defined above for formula I, more preferably as defined for formula II (wherein this R^3 group is the G-A-R-E-Y^2 substituent), and more preferably still as defined for formula III, and

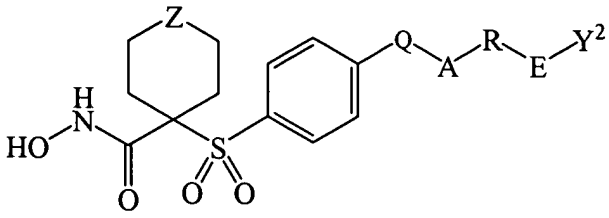
Please replace the paragraph bridging line 15 on page 27 to line 10 on page 28 with the following new paragraph:

Further compounds of formula A are also particularly preferred. One group of these compounds corresponds in structure to formula B (including formulas B, B-A, B-1, B-1A, B-2, B-2A, B-3 and B-3A), formula VIC, and more still particularly to formula VIC-1 and formula VIC-2, and formula VIII, below. In those formulas, ring structure Q is a substituent of the depicted phenyl ring and can itself be substituted. Substituent Q including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 7-members, preferably 6-members, and can contain zero or one additional nitrogen atom. The substituents of Q such as A-R-E-Y^2, R-E-Y^2 and E-Y^2 are as defined before, and such a substituent is bonded at the 4-position relative to that depicted nitrogen atom when Q is a 6- or 7-membered ring and at the 3- or 4- position relative to that depicted nitrogen when Q is a 5-membered ring. The remaining members of such a Q-bearing substituent (e.g., A-R-E-Y^2) are defined herein for the substituent G-A-R-E-Y^2. In addition, R^{20}, X, Y, Z, m, n, and p of the ring system and g are as before described, with Z preferably being O or NR^6.

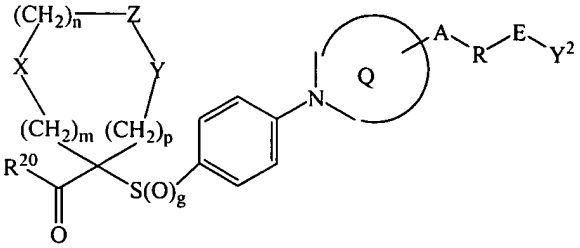
Please replace the structures from line 11 on page 28 to line 2 on page 30 with the following new structures:



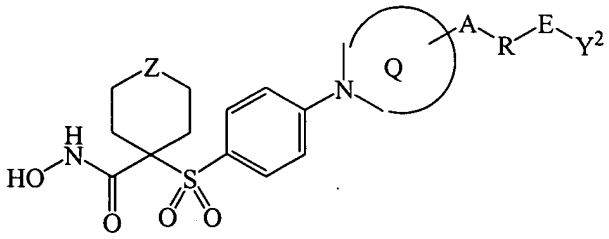
B



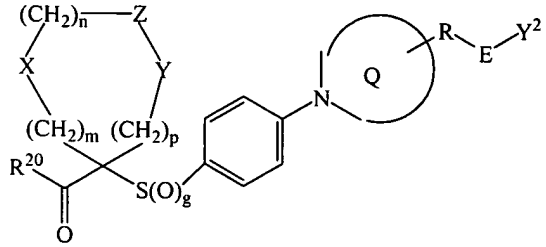
B-A



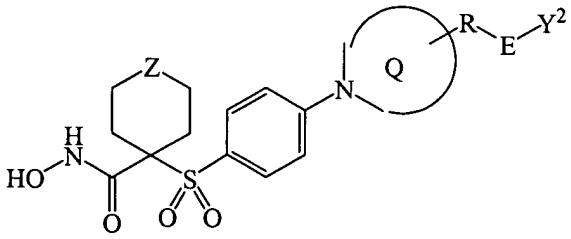
B-1



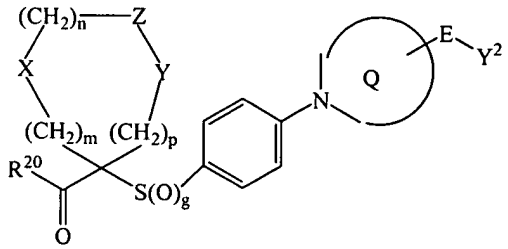
B-1A



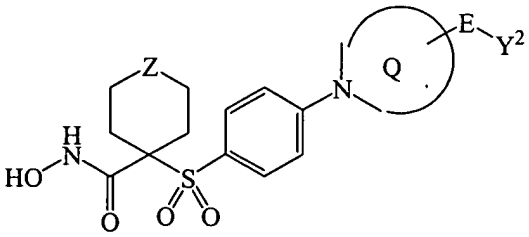
B-2



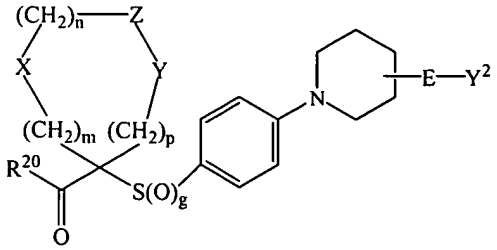
B-2A



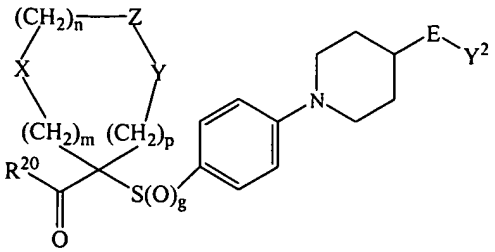
B-3



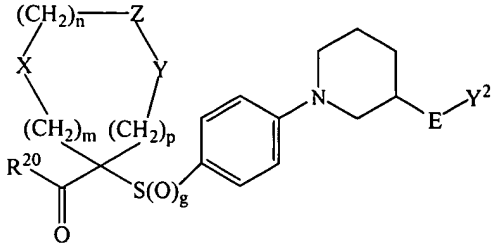
B-3A



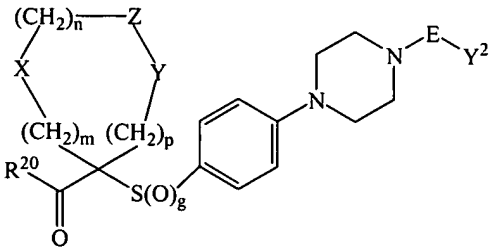
VIC



VIC-1



VIC-2

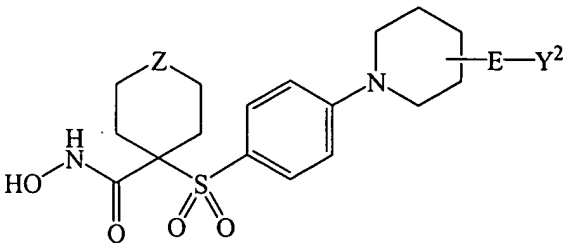


VIII

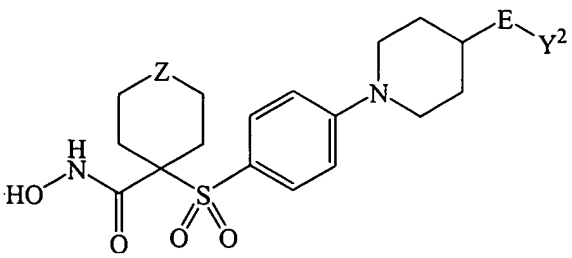
Please replace the paragraph bridging lines 3-17 on page 30 with the following new paragraph:

The compounds of formulas IX, IX-1, IX-2, X, XI, XI-1, XI-2 and XII, below, are more particularly preferred among the compounds of formula VIC, formula VIC-1, formula VIC-2, and formula VIII. In those latter formulas, Z is as before described, with Z preferably being O or NR^6, and substituent Q is a 6-membered ring, as is shown. The A moiety of the Q ring substituent -A-R-E-Y^2 (e.g. of formula B or B-1) is preferably absent in some embodiments, as in the compounds of formulas XI through XII, whereas both moieties A and R of that substituent group are absent in compounds of formulas IX through X. The moieties A, R, E and Y^2 of the substituent group -A-R-E-Y^2 are defined for the substituent group -G-A-R-E-Y^2.

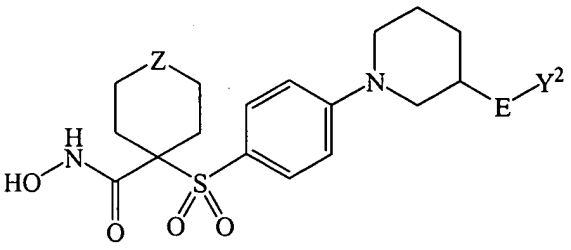
Please replace the structures from line 18 on page 30 to line 4 on page 31 with the following new structures:



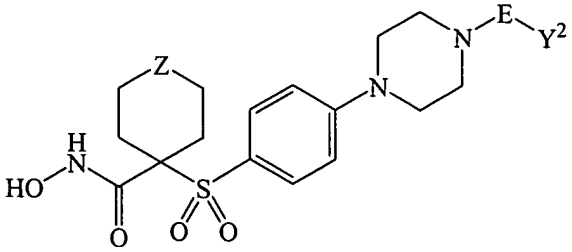
IX



IX-1



IX-2



X

Please replace the paragraph bridging lines 4-11 on page 32 with the following new paragraph:

wherein m, n, p, X, Z and Y are as defined above for formula II, g is zero, 1 or 2 and R^{24} is R^3 as defined in formulas I, III or IV, is the substituent G-A-R-E-Y^2 of formula II (formula VIA) or is $R^{3'}$, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.

Please replace the paragraph bridging line 29 on page 35 to line 9 on page 36 with the following new paragraph:

In accordance with the present invention, it has been discovered that certain aromatic sulfone hydroxamic acids (including hydroxamates) are effective for inhibition of matrix metalloproteinases ("MMPs") believed to be associated with uncontrolled or otherwise pathological breakdown of connective tissue. In particular, it has been found that these certain aromatic sulfone hydroxamic acids are effective for inhibition of one or more enzymes such as MMP-2, MMP-9 and MMP-13, which can be particularly destructive to tissue if present or

generated in abnormal quantities or concentrations, and thus exhibit a pathological activity. Included in that pathological activity is the assistance of tumors and tumor cells in the process of penetrating basement membrane, and developing a new or improved blood supply; i.e., angiogenesis.

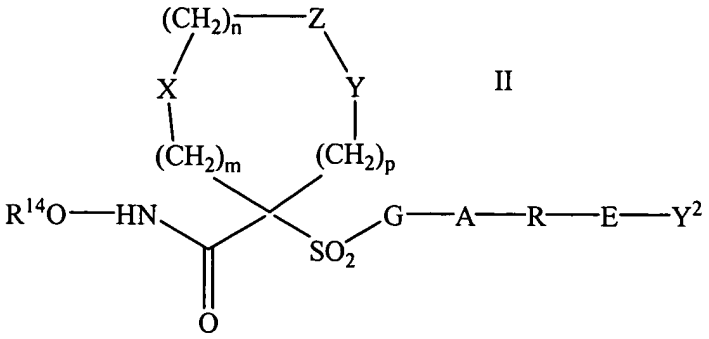
Please replace the paragraph bridging lines 10-25 on page 36 with the following new paragraph:

Moreover, it has been discovered that these aromatic sulfone hydroxamic acids are selective in the inhibition of one or more of MMP-2, MMP-9 and MMP-13 without excessive inhibition of other collagenases essential to normal bodily function such as tissue turnover and repair. More particularly, it has been found that a contemplated aromatic sulfone hydroxamic acid of the invention, or a pharmaceutically acceptable salt thereof, is particularly active in inhibiting of one or more of MMP-2, MMP-9 and MMP-13 in an *in vitro* assay that is predictive of *in vivo* activity. In addition, while being selective for one or more of MMP-2, MMP-9 and MMP-13, a contemplated aromatic sulfone hydroxamic acid, or its salt, has a limited or minimal *in vitro* inhibitory effect on MMP-1.

Please replace the paragraph bridging lines 16-31 on page 39 with the following new paragraph:

Thus, in one embodiment, the present invention is directed to a treatment process that comprises administering a contemplated aromatic sulfone hydroxamic acid metalloprotease inhibitor, or a pharmaceutically acceptable salt thereof, in an effective amount to a host mammal having a condition associated with pathological matrix metalloprotease activity. A contemplated aromatic sulfone hydroxamic acid inhibitor compound useful in such a process inhibits the activity of one or more of MMP-2, MMP-9 and MMP-13, and exhibits substantially less inhibitory activity against at least MMP-1 in the *in vitro* assay noted above and discussed in detail hereinbelow. An aromatic sulfone hydroxamic acid inhibitor compound for use in a contemplated process corresponds in structure to formula I, below:

Please replace Formula II at line 10 on page 46 with the following new Formula II:



Please replace the paragraph bridging line 27 on page 51 to line 4 on page 52 with the following new paragraph:

G-A-R-E-Y^2 is a substituent that preferably has a length greater than that of a pentyl group, and more preferably has a length greater than that of a hexyl group. The substituent G-A-R-E-Y^2 preferably has a length that is less than that of an icosyl group, and is more preferably less than that of a stearyl group. In this substituent:

Please replace the paragraph bridging lines 24-25 on page 53 with the following new paragraph:

(9) E is absent and R is bonded directly to Y^2; and

Please replace the paragraph bridging line 26 on page 53 to line 10 on page 54 with the following new paragraph:

the moiety Y^2 is absent or is selected from the group consisting of a hydrido, alkyl, alkoxy, haloalkyl, aryl, aralkyl, cycloalkyl, heteroaryl, hydroxy, aryloxy, aralkoxy, heteroaryloxy, heteroaralkyl, perfluoroalkoxy, perfluoroalkylthio, trifluoromethylalkyl, alkenyl, heterocycloalkyl, cycloalkyl, trifluoromethyl, alkoxycarbonyl, and a aminoalkyl group, wherein the aryl, heteroaryl, aralkyl, or heterocycloalkyl group is (i) unsubstituted or (ii) substituted with one or two radicals independently selected from the group consisting of an alkanoyl, halo, nitro, aralkyl, aryl, alkoxy, trifluoroalkyl, trifluoroalkoxy and an amino group wherein the amino nitrogen is (i) unsubstituted or (ii) substituted with one or two groups independently selected from hydrido, alkyl, and an aralkyl group.

Please replace the paragraph bridging lines 11-21 on page 54 with the following new paragraph:

The substituent -G-A-R-E-Y^2 preferably contains two to four carbocyclic or heterocyclic rings, including the aryl or heteroaryl group, G. More preferably, each of those rings is 6-membered. Additional separate preferences for a compound of formula II include: (a) that A is -O- or -S-, (b) R is an aryl, heteroaryl, cycloalkyl or heterocycloalkyl group, (c) E is absent, and (d) Y^2 is selected from the group consisting of hydrido, an alkyl, alkoxy, perfluoroalkoxy and a perfluoroalkylthio group.

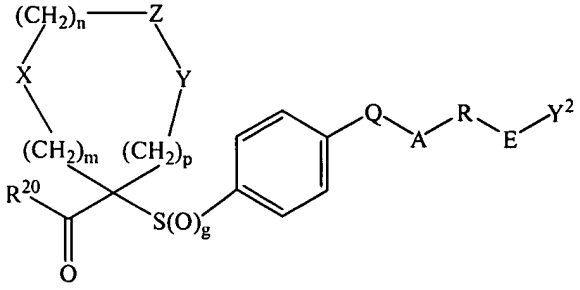
Please replace the paragraph bridging lines 3-7 on page 62 with the following new paragraph:

Here, R^3 is as defined above as to formulas I, III and more preferably as defined as to formula II (wherein the R^3 radical is the substituent G-A-R-E-Y^2). Most preferably, R^3 is as defined in formula III.

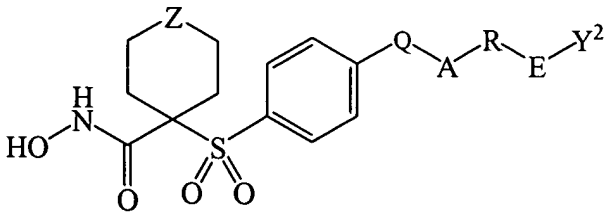
Please replace the paragraph bridging line 20 on page 63 to line 12 on page 64 with the following new paragraph:

Further compounds of formula A are also particularly preferred. One group of these compounds corresponds in structure to formula B, formula VIC, and more still particularly to formula VIC-1 and formula VIC-2, and formula VIII, below. In those formulas, ring structure Q including the depicted nitrogen atom is a heterocyclic ring that contains 5- or 7-members, preferably 6-members, and can contain zero or one additional nitrogen atom in addition to that depicted. The members of substituent -A-R-E-Y^2 (or -R-E-Y^2 or -E-Y^2) are as defined elsewhere in the definition of the members of the substituent -G-A-R-E-Y^2. Furthermore, substituent A-R-E-Y^2 (or substituent R-E-Y^2 or E-Y^2) is bonded at the 4-position relative to that depicted nitrogen atom when Q is a 6- or 7-membered ring and at the 3- or 4- position relative to that depicted nitrogen when Q is a 5-membered ring. Still further, R^{20}, X, Y, Z, m, n, and p of the ring system and g are as before described.

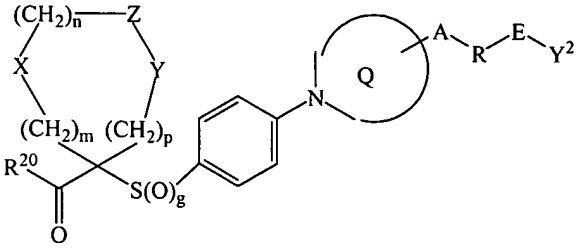
Please replace the structures from line 13 on page 64 to line 2 on page 66 with the following new structures:



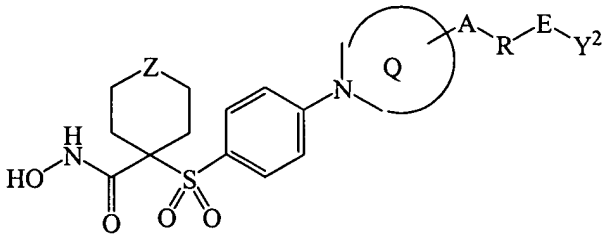
B



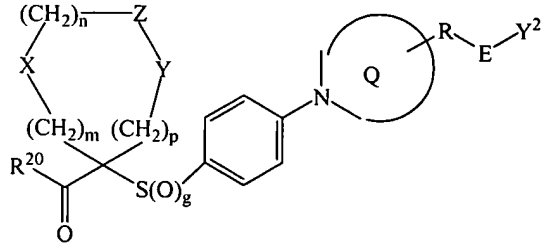
B-A



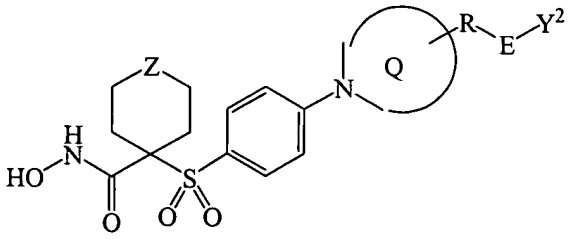
B-1



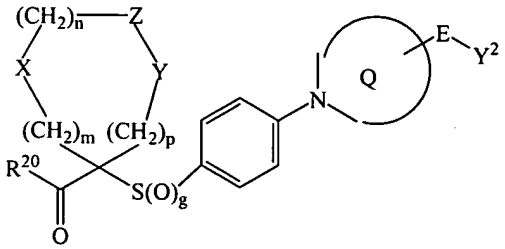
B-1A



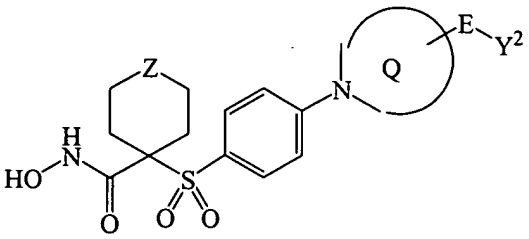
B-2



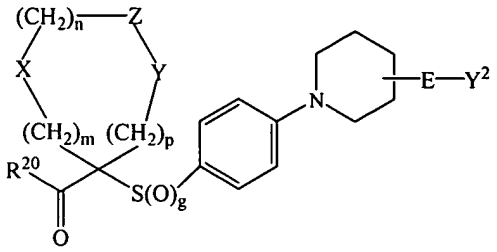
B-2A



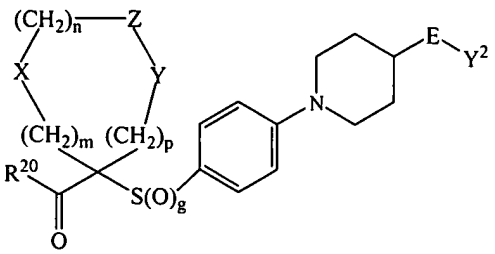
B-3



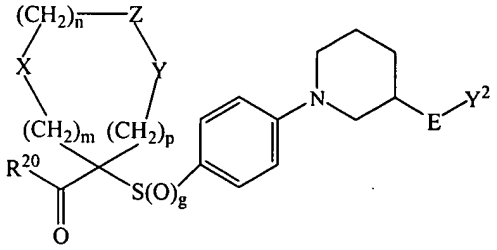
B-3A



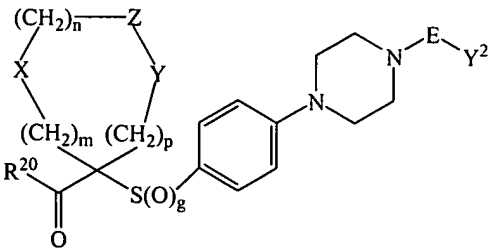
VIC



VIC-1



VIC-2

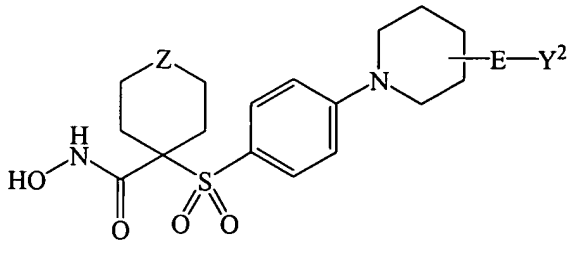


VIII

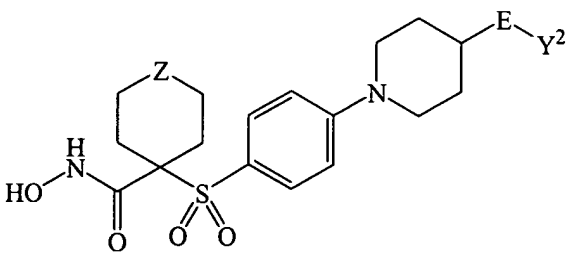
Please replace the paragraph bridging lines 3-9 on page 66 with the following new paragraph:

More particularly preferred among the compounds of formula VIC, formula VIC-1, formula VIC-2, and formula VIII, are the compounds of formulas B-2, IX, IX-1, IX-2, X, XI, XI-1, XI-2 and XII, below, wherein Z is as before described and the members of the substituent group -E-Y^2 and -R-E-Y^2 are defined for the substituent group -G-A-R-E-Y^2.

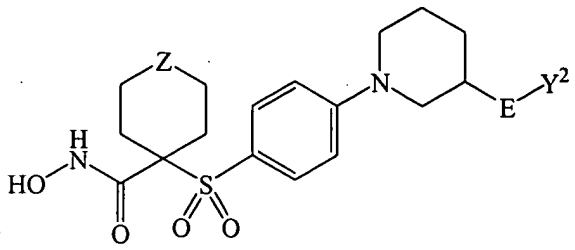
Please replace the structures from line 10 on page 66 to line 7 on page 67 with the following new structures:



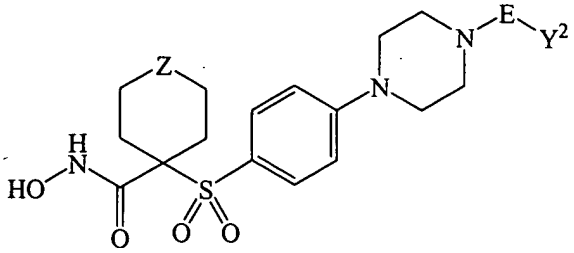
IX



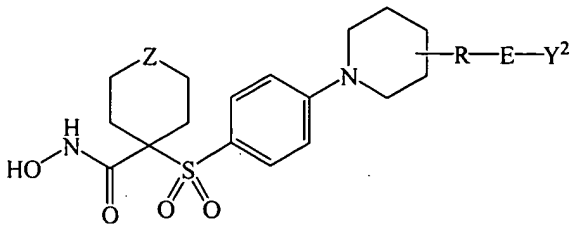
IX-1



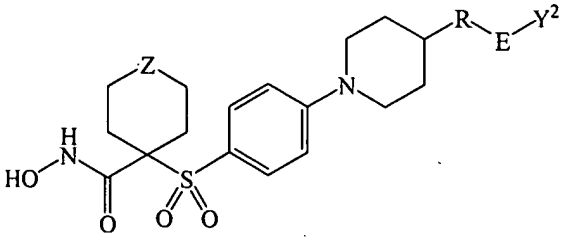
IX-2



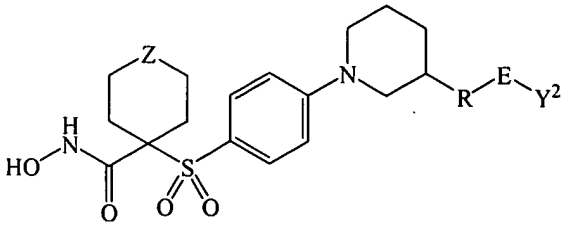
X



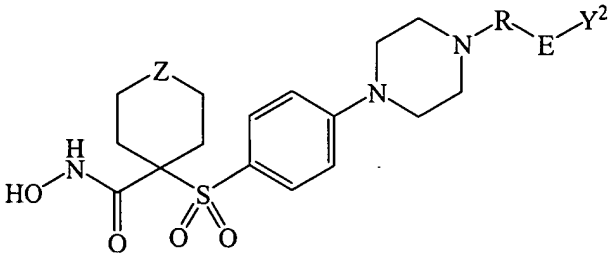
XI



XI-1



XI-2



XII

Please replace the paragraph bridging lines 12-26 on page 75 with the following new paragraph:

In one embodiment of a particularly preferred aromatic sulfone hydroxamic acid inhibitor compound, an R^{23} substituent is phenoxy and is itself substituted at its own para-position with a moiety that is selected from the group consisting of a halogen, a C_1-C_4 alkoxy group, a C_1-C_4 alkyl group, a dimethylamino group, a carboxyl C_1-C_3 alkylene group, a C_1-C_4 alkoxy carbonyl C_1-C_3 alkylene group, a trifluoromethylthio group, a trifluoromethoxy group, a trifluoromethyl group and a carboxamido C_1-C_3 alkylene group, or is substituted at the meta- and para-positions by a methylenedioxy group. It is to be understood that any R^{23} substituent can be substituted with a moiety from the above list. Such substitution at the para-position is preferred.

Please replace the paragraph bridging lines 8-14 on page 82 with the following new paragraph:

R^{24} is R^3 as defined in formulas I, III, IV or is the substituent G-A-R-E-Y^2 of formula II (formula VIA). Alternatively, R^{24} is $R^{3'}$, an aryl or heteroaryl group that is substituted with a coupling substituent reactive for coupling with another moiety (formula VIB), such as a nucleophilically displaceable leaving group, D.

Please replace the paragraph bridging line 17 on page 82 to line 10 on page 83 with the following new paragraph:

Exemplary nucleophilically displaceable leaving groups, D, include a halo (fluoro, chloro, bromo, or iodo) nitro, azido, phenylsulfoxido, aryloxy, C_1-C_6-alkoxy, a C_1-C_6-alkylsulfonate or arylsulfonate group and a trisubstituted ammonium group in which the three substituents are independently aryl, ar- C_1-C_6-alkyl or C_1-C_6-alkyl. Additional coupling substituents include, without limitation, a hydroxyl group and an amino group that can be coupled with carbonyl-containing moieties to form esters, urethanes, carbonates, amides and ureas. Similarly, a carboxyl coupling substituent can be used to form an ester, thioester or amide. Thus, a coupling substituent is useful in converting a coupling substituent-containing aryl or heteroaryl group into a substituent such as a G-A-R-E-Y^2 substituent discussed hereinabove by the formation of a covalent bond.

Please replace the paragraph bridging lines 11-18 on page 83 with the following new paragraph:

A compound of formula VI can be coupled with another moiety at the $R^{3'}$ coupling substituent to form a compound whose newly formed R^3 group is that of formulas I, III, IV or -G-A-R-E-Y^2. Exemplary of such couplings are the nucleophilic displacement to form ethers and thioethers, as well as the formation of ester, amide, urea, carbonate, urethane and the like linkages.

Please replace the paragraph bridging lines 13-22 on page 96 with the following new paragraph:

The term "aminocarbonyl" (carboxamide) alone or in combination, means an amino-substituted carbonyl (carbamoyl) group derived from an amine reacted with a carboxylic acid wherein the amino (amido nitrogen) group is unsubstituted ($-NH_2$) or a substituted primary or secondary amino group containing one or two substituents selected from the group consisting of hydrogen, alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like, as recited. A hydroxamic acid is a N-hydroxycarboxamide.

Please replace the paragraph bridging line 25 on page 97 to line 15 on page 98 with the following new paragraph:

The term "pharmaceutically acceptable" is used adjectivally herein to mean that the modified noun is appropriate for use in a pharmaceutical product. Pharmaceutically acceptable cations include metallic ions and organic ions. More preferred metallic ions include, but are not limited to appropriate alkali metal (Group Ia) salts, alkaline earth metal (Group IIa) salts and other physiologically acceptable metal ions. Exemplary ions include aluminum, calcium, lithium, magnesium, potassium, sodium and zinc in their usual valences. Preferred organic ions include protonated amines and quaternary ammonium cations, including in part, trimethylamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine) and procaine. Exemplary pharmaceutically acceptable acids include without limitation hydrochloric acid, hydrobromic acid, phosphoric acid, sulfuric acid, methanesulfonic acid, acetic acid, formic acid, tartaric acid, maleic acid, malic acid, citric acid, isocitric acid, succinic acid, lactic acid, gluconic acid, glucuronic acid, pyruvic acid oxalacetic acid, fumaric acid, propionic acid, aspartic acid, glutamic acid, benzoic acid, and the like.

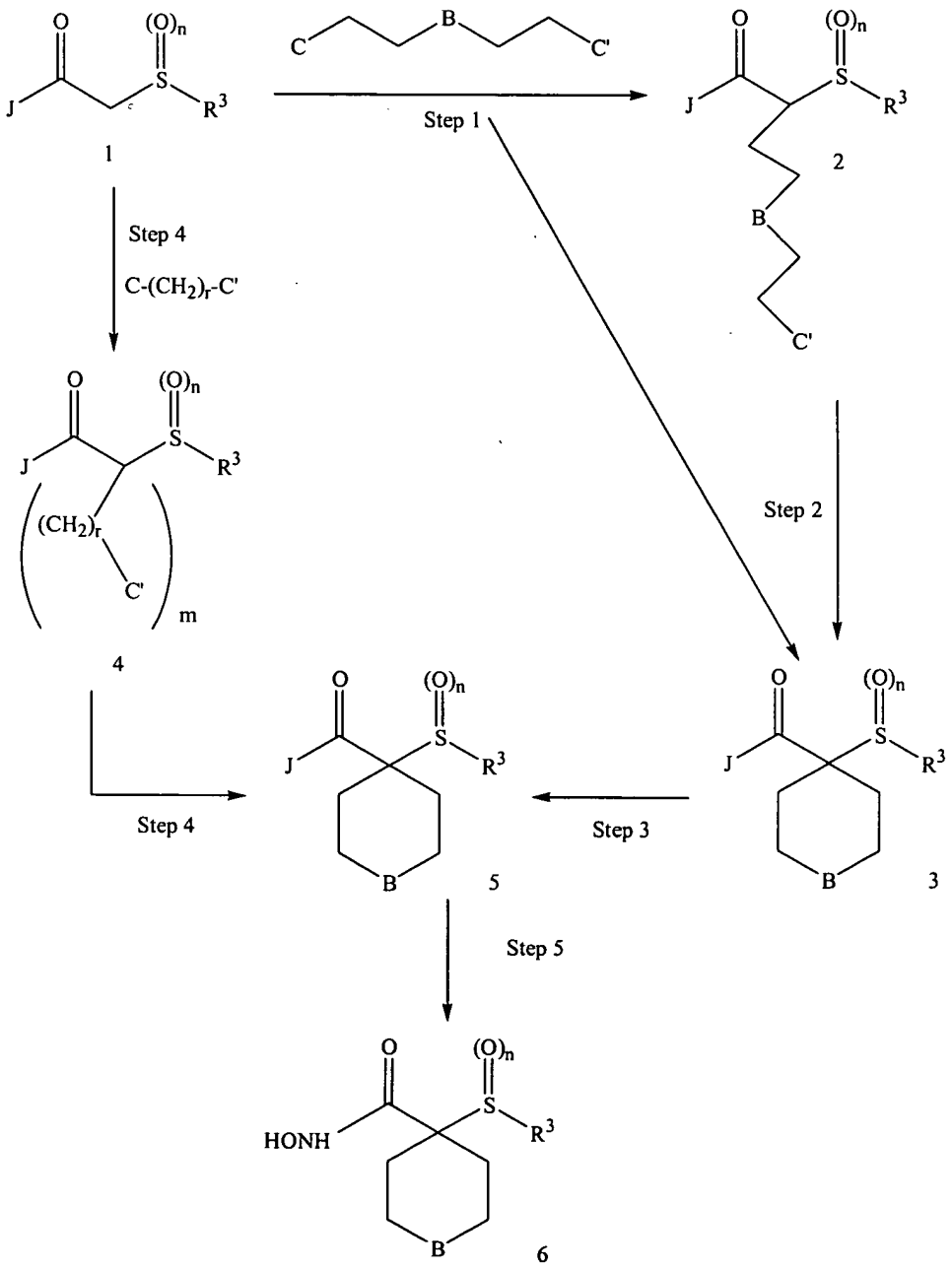
Please replace the paragraph bridging lines 23-30 on page 99 with the following new paragraph:

The structures in Schemes 1 through 19 are also shown with compounds that represent the other compounds of this invention. The aromatic ring in Scheme C is aryl and heteroaryl.

The moieties of -A-R-E-Y^2 are as defined before. Reactions illustrated involving a spiroheterocyclic nitrogen atom may not be applicable to those compounds with sulfur or oxygen.

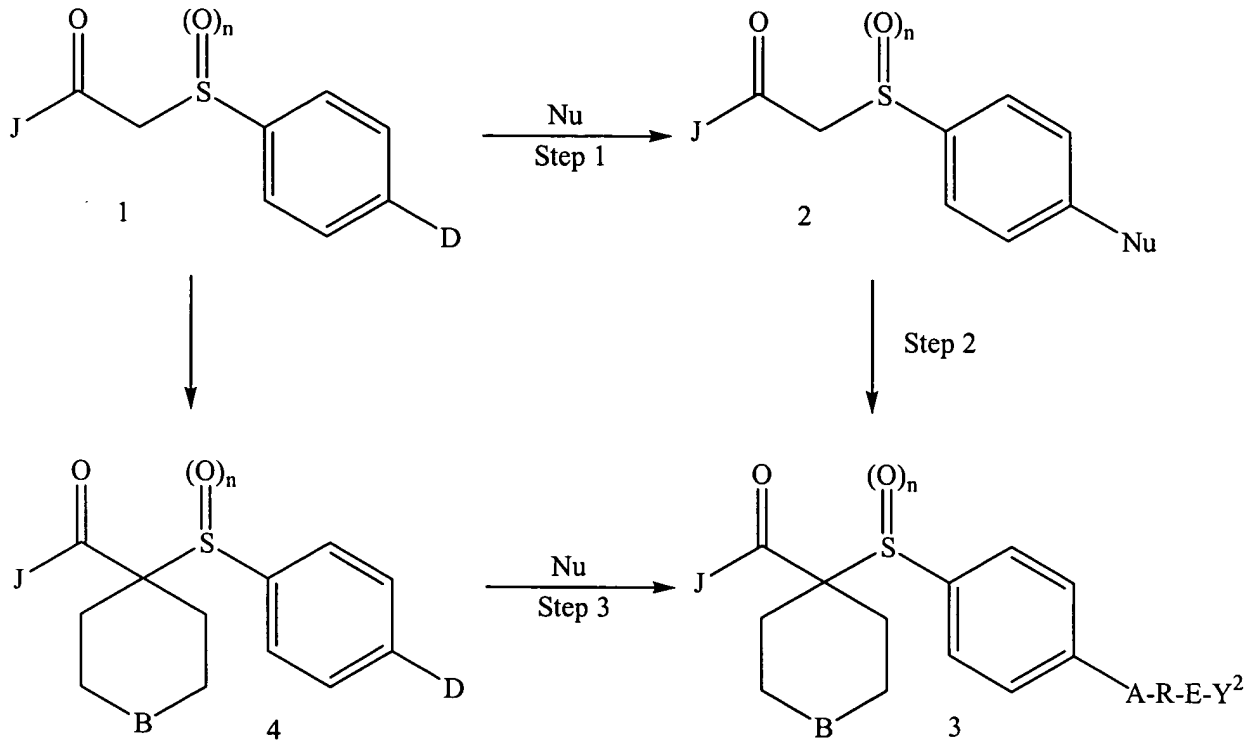
Please replace Scheme B at line 1 on page 104 with the following new Scheme B:

Scheme B



Please replace Scheme C at line 17 on page 106 with the following new Scheme C:

Scheme C



Please replace the paragraph bridging lines 13-18 on page 107 with the following new paragraph:

Steps 1, 2 and 3 also illustrate that although the nucleophilic displacement can be carried out with one nucleophile (Nu), the product of this reaction can be modified by methods well known in the art and as shown herein to provide the group -A-R-E-Y^2 as defined hereinbefore.

Please replace the paragraph bridging lines 19-31 on page 107 with the following new paragraph:

A non-limiting illustration of such a process is provided when D is fluoride. The fluoride leaving group can be directly displaced with the anion of 4-trifluoromethylphenol, 4-trifluoromethoxyphenol, 4-trifluoromethylthiophenol and the like to provide a contemplated compound. This is a one pot process from Compound 4. Other compounds included in -A-R-E-Y^2 can be prepared by displacing the fluoride leaving group with ammonia to provide an

amine, which can then be acylated by methods discussed wherein with, for example, 4-trifluoromethylbenzoyl chloride, to form another contemplated product compound.

Please replace the paragraph bridging line 23 on page 407 to line 2 on page 408 with the following new paragraph:

Part A: A solution of the hydroxamate of Example 233, part F (50 mg, 0.08 mmol) in water (2 mL) was neutralized with saturated sodium bicarbonate. The aqueous solution was extracted with ethyl acetate. Concentration *in vacuo* provided the hydroxamic acid free base as an orange solid (35 mg, 75%).

Please replace the paragraph bridging line 13 on page 521 to line 3 on page 522 with the following new paragraph:

More specifically, recombinant human MMP-13, MMP-1, MMP-2 and MMP-9 enzymes were prepared in laboratories of the assignee following usual laboratory procedures. MMP-13 from a full length cDNA clone was expressed as a proenzyme using a baculovirus as discussed in V.A. Luckow, Insect Cell Expression Technology, pages 183-218, in Protein Engineering: Principles and Practice, J.L.Cleland et al eds., Wiley-Liss, Inc., (1996). See, also, Luckow et al., *J. Virol.*, 67(8):4566-4579 (1993); O'Reilly et al., Baculovirus Expression Vectors: A Laboratory Manual, W.H. Freeman and Company, New York, (1992); and King et al., The Baculovirus Expression System: A Laboratory Guide, Chapman & Hall, London (1992) for further details on use of baculovirus expression systems. The expressed enzyme was purified first over a heparin agarose column and then over a chelating zinc chloride column. The proenzyme was activated by APMA for use in the assay.

Please replace the paragraph bridging lines 4-28 on page 522 with the following new paragraph:

MMP-1 expressed in transfected HT-1080 cells was provided by Dr. Harold Welgus of Washington University, St. Louis, MO. The enzyme was also activated using APMA and was then purified over a hydroxamic acid column. Dr. Welgus also provided transfected HT-1080 cells that expressed MMP-9. Transfected cells that expressed MMP-2 were provided by Dr.

Gregory Goldberg, also of Washington University. Studies carried out using MMP-2 in the presence of 0.02% 2-mercaptoethanol are shown in the table below with an asterisk. Studies with MMP-7 were carried out at pH 7.5 in the presence of 0.02% 2-mercaptoethanol using conditions otherwise similar to those used for the other enzymes. The enzyme was obtained from a hMMP-7-expressing E. coli clone that was a gift of Dr. Steven Shapiro of Washington University, St. Louis, MO. Further specifics for preparation and use of these enzymes can be found in the scientific literature describing these enzymes. See, for example, Enzyme Nomenclature, Academic Press, San Diego, Ca (1992) and the citations therein, and Freije et al., J. Biol. Chem., 269(24): 16766-16773 (1994). The enzyme substrate is a methoxycoumarin-containing polypeptide having the following sequence:

Please replace the paragraph bridging lines 4-11 on page 549 with the following new paragraph:

The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See*, Kenyon, BM, et al., *A Model of Angiogenesis in the Mouse Cornea*, Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8, pp. 1625-1632.